AMENDMENTS TO THE DRAWINGS

The attached sheets of drawings include changes to Figures 1A and 1B.

Attachment: Replacement sheet
Annotated sheet showing changes

REMARKS

Status of the claims

Claims 1-7, 9-28 and 30-45 are pending in the application. Claims 3-7, 9-28, 30-34, and 37-41 are amended herein. Claims 1-2, 16-26, 31-36 and 38-43 are withdrawn. Claims 8 and 29 are cancelled and claims 44 and 45 are newly added. Support for new claim 44 may be found at least in original claim 4 and in Example 1, found on page 26, line 5 through page 29, line 20 of the specification. Support for new claim 45 may be found at least in original claims 17 and 24 and in Examples 1 and 2 found, respectively, on page 26, line 5 through page 29, line 20 and page 32, line 20 through page 33, line 18 of the specification. No new matter has been added with the amendments or new claims. As such, entry and consideration thereof are respectfully requested.

Restriction requirement

Applicants note that the Examiner has rejoined Groups III and IV and replaced the restriction with an election of species. The Examiner further considers the elected species to be the IL-15 agonist. Applicants request rejoinder of the species of IL-15 antagonist, as well as any claims directed to making or using the elected invention (at least Groups VII-IX) upon a finding of the novelty and unobviousness of the elected species.

Applicants further note that claims 4-33, 37, 44 and 45 are directed to the elected invention. Of these claims, claims 4-15, 27-30, 37, 44 and 45 read on the elected species. As such consideration of all of these claims is respectfully requested. Claims 16-26 and 31-33 read upon the non-elected species. However, since the elected species has been found patentable over the prior art, the Examiner should now also consider the non-elected species and examine claims 16-26 and 31-33.

Formal matters

1) *Information Disclosure Statement* – The Examiner notes that the PTO Form SB-08 submitted on January 30, 2007, indicates that there are three total pages but only two pages are in the file-wrapper of the application. Applicants note that the PTO Form SB-08 contains a typographical error and there are, in fact, only two pages to the document. Thus, the record is complete.

2) *Objections to the Drawings and sequences* – The Examiner objects to the drawings noting that Fig. 1 A, which has 114 amino acids, references SEQ ID NO:2, but SEQ ID NO:2 has 162 amino acids. In addition, the Brief Description of the Drawings on page 5 references SEQ ID NO:2. Fig. 1A and the specification have been corrected to indicate that the sequence of Fig. 1A depicts amino acids 49-162 of SEQ ID NO:2 rather than the entire sequence.

In addition, the Examiner notes that for Fig. 1B, the number "45" is misplaced on top of "L44" instead of "L45". Fig 1B has been appropriately corrected.

3) *Objections to the specification* - The specification has been objected to for containing embedded hyperlinks on page 10, line 3 and page 20, line 26. The specification has been amended, as indicated above, to remove the hyperlinks.

4) *Objections to the claims* - Claims 8-15, 27-30 and 37 have been objected to as being improperly dependent. The claims have been amended to address and correct any dependency errors.

Claims 4-7 have been further objected to for reciting "IL-15 mutein" rather than "An IL-15 mutein". Claims 4-7 have been amended to address this issue.

Rejections under 35 U.S.C.§112, 2nd paragraph

Claims 4-7 have been rejected under 35 U.S.C.§112, 2nd paragraph as being indefinite. More specifically claim 4 has been rejected for recitation of "at least one....addition with in the region spanning", with the assertion that the upper limit is undefined. The claims have been amended to delete recitation of "at least". Withdrawal of the rejection is respectfully requested.

Claims 4 and 5 have been further rejected as being indefinite in the recitation of "not significantly different from" with the assertion that the phrase is a relative term. The claims have been amended to delete recitation of "significantly". Withdrawal of the rejection is therefore respectfully requested.

Rejections under 35 U.S.C.§112, 1st paragraph

Claims 4-7 have been rejected under 35 U.S.C.§112, 1st paragraph with the assertion that the specification is only enabled for claims limited to an IL-15 mutein having one substitution at L45, Q48, V49, S51 or L52 or having one substitution within the region spanning residues 64-69, wherein the IL-15 retains the binding affinity for IL-15Rα.

The Examiner asserts that the specification fails to teach any other sequence modifications other than those discussed above. Applicants traverse this rejection in as much as it may be in any way applied to the amended claims and withdrawal thereof is respectfully requested.

Claim 4 – Claim 4, as amended, is directed to an IL-15 mutein, having a sequence that is derivable from human mature wild-type IL-15 by one substitution within the region spanning from residue 44 to residue 52, or from residue 64 to residue 68, or from residue 64 to residue 69, provided that the IL-15 mutein resulting therefrom has an affinity for binding to IL-15Ralpha that is either not different from, or is higher than the affinity of human mature wild-type IL-15 for binding to IL-15Ralpha.

Thus, the invention of claim 4 is directed to an IL-15 mutein having one substitution in the region spanning residues 44-52 or 64-69. One skilled in the art could readily, without undue experimentation, practice the invention as claimed. Claim 4, as amended, only encompasses a substitution at one of 15 positions within the IL-15 sequence. Thus, claim 4 is directed to a limited number of well-defined IL-15 muteins.

In addition, one skilled in the art can easily verify whether a substation when made at one of the 15 positions has an affinity that is not different from or higher than the affinity of mature wild-type IL-15 for binding to IL-15Rα, by, for example, simply using the IL-15 binding assay disclosed on page, 24, line 27 through page 25, line 18 of the specification.

The skilled artisan can also readily verify whether the IL-15 mutein is an IL-15 agonist or IL-15 antagonist by simply using, for example, the proliferation assays disclosed on page 24, line 27, through page 25, line 18 of the specification.

The present inventors found that the regions spanning from residue 44 to residue 52 and from residue 64 to residue 69 are involved in the binding of IL-15 to the IL-15Rα. The region spanning from residue 64 to residue 69 is also involved in the recruitment of IL-15ß (see page 30, line 10, page 31, lines 18-20 and page 32, lines 9-10 of the specification). This teaching provides guidance to one skilled in the art for obtaining muteins that have an affinity for IL-15Rα that is either not different from or is higher than the affinity of mature wild-type IL-15.

Further, the specification provides nine working examples of IL-15 muteins having one substitution, and having an affinity for IL-15Rα that is not different from or higher than the affinity of mature wild-type IL-15 (see Table 1 on page 27 and Table III on page 34). Among the nine working examples, five of the muteins were IL-15 agonists and four were IL-15 antagonists.

Finally, on page 12, lines 5-9, the specification provides clear guidance as to appropriate substitutions that may be made.

As such, contrary to the abstract assertions of the Examiner, the specification provides clear guidance and numerous working examples for how to practice the invention, which is itself limited to only a single substitution at only 15 positions. As such, the invention as claimed is fully enabled and withdrawal of the rejection is respectfully requested.

Claim 5 – Claim 5, as amended, is directed to the IL-15 mutein of claim 4 which is limited to a single mutation within the region spanning from residue 44 to residue 52. The specification discloses four IL-15 muteins having one substitution within the region spanning from residue 44 to 52 and having and affinity for IL-15Rα that is either not different from or is higher than the affinity of mature wild-type IL-15, and which are IL-15 agonists. See Table 1 on page 27 and Table II on page 28 of the specification.

One skilled in the art could readily obtain additional such muteins. In particular, the specification as filed provides guidance regarding appropriate substitutions, which may be made. See page 12, lines 5-9. In addition, as noted above, the skilled artisan can also readily verify whether the IL-15 muteins are IL-15 agonists by using, for example, the proliferation assays disclosed on page 24, line 27, through page 25, line 18 of the specification. As such, the invention of claim 5 is fully enabled and withdrawal of the rejection is respectfully requested.

Claims 6-15, 27-30 and 37 - Claims 6-15, 27-30 and 37 depend from claim 4 or 5 and thus have all the limitations of claims 4 and 5. Claims 6-15, 27-30 and 37 are thus similarly enabled.

Claim 44- New claim 44 recites that the substitution is specifically at one of residues 45, 48, 51, 52, 64, 65, 68 or 69. The muteins of claim 44 are fully supported and enabled by the data in the specification. The inventors have shown that substitutions at any one of these positions results in a IL-15 mutein that (i) has an affinity for IL-15Rα that is higher than the affinity of mature wild-type IL-15 for binding to IL-15Rα (see Table 1 on page 27 and Table III on page 34) and (ii) are either IL-15 agonists or IL-15 antagonists (see Table II on page 28 and page 34, lines 8-13). Thus, claim 44 is fully enabled as claimed.

Claim 45 - New claim 45 recites that the substitution is specifically at one of residues 45, 48, 51, or 52. The muteins of claim 45 are fully supported and enabled by the data in the specification. The inventors have shown that substitutions at any one of these four positions results in a IL-15 mutein that (i) has an affinity for IL-15Rα that is higher than the affinity of mature wild-type IL-15 for binding to IL-15Rα (see Table 1 on page 27 and Table III on page 34) and (ii) are either IL-15 agonists or IL-15 antagonists (see Table II on page 28 and page 34, lines 8-13). Thus, claim 45 is fully enabled as claimed.

In view of the above amendments and Remarks, Applicants believe the pending application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact MaryAnne Armstrong, PhD, Reg. No. 40,069 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

By _____

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Attachments: Drawings